REMARKS

Objection to Title of the Invention

The Examiner has objected to the Title of the Invention for not being clearly indicative of the invention to which the claims are directed. In response to the Examiner's request, the Applicants request that the following Title be substituted: METHOD FOR DELAYING PRETERM UTERINE CONTRACTIONS IN A PREGNANT MAMMAL.

Objection to the Abstract of the Invention

The Examiner has objected to the Abstract of the Invention for not being directed towards the invention to which the claims are directed. In response to the Examiner's request, the Applicants request that the following Abstract be substituted:

> Disclosed herein are novel methods for delaying preterm uterine contractions in a pregnant mammal utilizing kinase inhibitors such as U0126, PD98059 and PD18432. In activation of the MAPK ERK cascade by, for example, the administration of kinase inhibitors such as U0126, PD98059 and PD18432 is disclosed as a novel method for delaying labor. Activation of the MAPK ERK pathway is disclosed as a novel method for inducing labor.

Interview with Examiner Phyllis Spivack

Applicants wish to thank Examiner Spivack for her courtesy and cooperation during the interview conducted on August 17, 2006. During the above-noted interview, Applicants' representative discussed the pending novelty and obviousness rejections with Examiner Spivack. Applicants' representative stated that they would study the rejections and respond in writing.

Claims 1 – 3 and 5 – 10 are not Anticipated Under 35 USC 102(b)

Claims 1 – 3 and 5 – 10 have been rejected under USC § 102(a) as being anticipated by Nohara, *et al.* The Examiner states "Nohara teaches the administration of MEK inhibitor PD098059 to cultured pregnant rat uterine cell obtained at day 21 before the onset of labor (preterm)." Office Action dated 08/03/2006, page 4. The Applicants respectfully traverse this rejection.

It is well settled law that under 35 USC 102, anticipation "requires that each and every element of the claimed invention be disclosed [either expressly or inherently] in the prior art ... [I]n addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." *Akzo N.V. v. U.S. International Trade Commission*, 1

USPQ 2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987); MPEP 2131. And, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP 2131. The Applicants submit that the Examiner has failed to meet this burden.

Claim 1 of the pending application is directed towards "... delaying preterm uterine contractions in a pregnant mammal through the administration of an effective amount of a compound which inhibits kinase activity ... thereby resulting in decreased levels of phosphorylated ERK in the pregnant mammal ...". The Applicants state clearly in the Background section of the pending application:

> Thus, it has not been possible by simple *in vitro* experiments to determine whether there is a cause and effect relationship between *gestation-dependent* activation of the ERK/CaD pathway and regulation of uterine contractility. The *in vivo* effect of ERK inhibition on modulating smooth muscle contractility *has not been previously explored. Emphasis added.* Pending Application, paragraph [0004].

and, in the Detail Description of the pending application:

> The present invention provides the first *in vivo* evidence for the involvement of the ERK MAPK in smooth muscle regulation. Pending Application, paragraph [0018].

The Applicants submit, without the teaching the element of a pregnant mammal the Nohara reference cannot be anticipatory because it does not teach each and every element of the pending claims either expressly or inherently, as is required by law. This is because Nohara, *et al.*, did not use pregnant mammals as was done in the pending application (*see*, for example, paragraph [0040} of the published US application 2005/0014676). Nohara, *et al.*, used cells isolated by enzymatic treatment from rat uterine myometrial tissue and cultured for five days before any experiments were performed. In contrast, the work by the present Applicants was performed *in vivo* in pregnant mammals. Nohara, *et al.*, do not teach this important element of pending Claim 1.

Furthermore, the Nohara reference does not inherently teach the pending claimed invention of delaying labor in a pregnant animal. The differences between the present invention and the work cited by the Examiner are extremely significant. Uterine cells, like other smooth muscle cells, undergo striking morphological and physiological changes when placed in culture. As noted by Palmberg and Thyberg these changes take place almost immediately upon placing the cells in culture. Palmberg and Thyberg, Cell and Tissue Res, 246(2):253-262, 1986. As with the Nohara reference relied upon by the Examiner, Palmberg and Thyberg used

enzymatically isolated uterine smooth muscle cells (SMC) from rat and also from humans. In regards to the morphological and physiological changes that take place in the cells once they are put into culture they state:

> During the first few days in culture the cells spread out on the substrate and went through a morphological transformation including loss of myofilaments followed by formation of an extensive rough endoplasmic reticulum and a large Golgi complex. Actin filaments aggregated in stress fibers spanning the entire length of the cells and microtubules and intermediate filaments formed a radiating system originating in the juxanuclear region. Abstract.

and, furthermore, in contrast to cells *in vivo*;

> The structural modification of the uterine SMC was accompanied by activation of cell growth. DNA synthesis was initiated already on day 1 ... page 259.

Thus, the prior art reference demonstrates conclusively that uterine cells in primary culture are morphologically and physiologically different from *in vivo* uterine cells. That cultured uterine cells are so markedly different from *in vivo* uterine cells in both morphology and physiology, one cannot assume that responses observed *in* vitro disclose either explicitly or inherently the *in* vivo methods discovered by inventors.

Furthermore, unlike cultured cells, cells studied *in vivo* are subject to natural physiological events such as, for example, exposure to various hormones of the animal. These types of factors are difficult if not down right impossible to duplicate accurately in culture. In fact, the references cited by the Examiner did not even address such factors. Thus, the references cite by the Examiner cannot possibly be considered prior art sufficient for an anticipation rejection for the pending claims.

In view of the proffered arguments, the Applicants respectfully request that the pending rejection be withdrawn.

Claims 1 – 11 are not Obvious Under 35 USC 103(a)

Claims 1 – 11 have been rejected under 35 USC 103 (a) as unpatentable over Nohara, *et al.*, in view of Oldenhof, *et al.* The Examiner states "Nohara teaches the administration of MEK inhibitor PD98059 to cultured pregnant rat uterine cells obtained at day 21 before the onset of labor (preterm)." Office Action dated 08/03/2006, page 4. The Examiner continues, "Nohara fails to mention the selective MAPK inhibitor U-0126. However, Oldenhof teaches the inhibitors PD-98059 and U-0126 as exhibiting essentially equivalent activity with respect to MAPK inhibition ...." Office Action dated 08/03/2006, page 4. The Applicants respectfully traverse this rejection.

The Examiner is reminded that a *prima facie* case of obviousness requires citation to a combination of references which (1) disclose the elements of the claimed invention, (2) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (3) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitle an applicant to allowance of the claims in issue. *See, e.g., Northern Telecom, Inc. v. Datapoint Corp.*

Applicants respectfully submit the Examiner has failed to establish any of these three elements of a *prima facie* case of obviousness. In addressing this rejection, Applicants directs their remarks to independent Claims 1 and 5. Claims 2 - 4 and 6 – 11 are dependent therefrom, respectively, and are *per se* non-obvious if independent Claims 1 and 5 from which they depend are not obviousness. *See*, MPEP 2143.03.

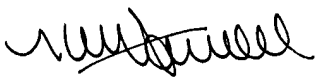
The cited references do not teach every element of the claimed invention. "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). MPEP2143.03. Nohara, as discussed above, does not teach the critical element of administering the taught inhibitors to pregnant mammals. Oldenhof, like Nohara, also uses cultured, isolated SMC. Therefore, Oldenhof does not supply this element that is missing form Nohara. Thus, the combination of Nohara and Oldenhof are deficient in teaching every element of the claimed invention as is required by law for an obviousness rejection.

Additionally, even if improperly combined, the references cited by the Examiner do not suggest a motivation to combine nor do they provide a reasonable expectation of success. Thus, the Applicants submit that the invention, as claimed, is non-obvious and respectfully request that the pending rejection be withdrawn.

Summary

In light of the above amendment and remarks, reconsideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,



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